thalamic nucleus. Roof *et al.* (1997) administered progesterone to rats following a frontal contusion and found that approximately one-third of 8-isoPGF$_{2\alpha}$ found in control rats. Roof *et al.* (1997) asserts that this data supports that progesterone has antioxidant effects. None of these references by Roof *et al.* teach or suggest the administration of allopregnanolone to treat a traumatic CNS injury or reduce neurodegeneration following a traumatic CNS injury.

Gee *et al.* (RE. 35,517) provide methods for modulating brain excitability to alleviate stress, anxiety, and seizure activity using certain progesterone derivatives. Gee *et al.* provide no teaching or suggestion that any progesterone derivative could be successfully used to treat a traumatic CNS injury.

And finally, the Examiner points to page 2, lines 10-15 of the instant specification which states that progesterone metabolites, such as allopregnanolone, are positive modulators of the GABA receptor.

The Examiner concludes that in view of the art cited and Applicants admissions, one of ordinary skill in the art would have reasonably expected that allopregnanolone would be useful to treat a traumatic central nervous system injury and decreasing neurodegeneration following a traumatic injury to the CNS as claimed by the present invention. Applicants submit that the Examiner has failed to establish a *prima facie* case of obviousness.

First, the Examiner acknowledges that the prior art does not disclose the use of allopregnanolone in a method of treating a traumatic central nervous system injury or a method of decreasing neurodegeneration in a subject following a traumatic injury to the CNS (page 3, Office Action mailed 4/23/02). The Examiner, however, asserts that Applicants admission on page 2 of the specification "teaches that the particular progesterone metabolite, allopregnanolone, also has neuroprotective properties modulating [the] GABA receptor and increasing the effects of GAGA, same as progesterone. See page 2 lines 10-15 [of the specification]." The Examiner further asserts that the "[a]pplicant's admission regarding the prior art also teaches that a traumatic brain injury to the CNS is tightly associated with GABA." Applicants respectfully disagree with the Examiner's conclusions.

The Examiner's attention is drawn to page 2, lines 28-31 of the specification which states "Following a traumatic injury to the central nervous system, *a cascade of physiological events leads to neuronal loss* including, for example, an inflammatory immune response and excitotoxicity resulting from the initial impact disrupting the glutamate, acetylcholine, cholinergic, $GABA_A$, and NMDA receptor systems. In addition, the traumatic CNS injury is frequently followed by brain and/or spinal cord edema that enhances the cascade of injury and leads to further secondary cell death and increased patient mortality" (emphasis added). Consequently, it is recognized that a traumatic injury to the CNS results in *multiple physiological events* that impact the extent and rate of neurodegeneration and thus the final outcome of the injury. While the specification discusses that the $GABA_A$ receptor systems may play a role in a traumatic injury to the CNS, it is hardly the only physiological event leading to the neuronal damage. Consequently, the Examiner's conclusion that the Applicants have provided an admission that a "traumatic brain injury to the CNS is know to be *tightly* associated with the GABA according to the prior art" (page 4, lines 14-15, Office Action mailed 4/23/01, emphasis added) is incorrect.

Furthermore, a *prima facie* case of obviousness requires the prior art to suggest the claimed invention without reference to the Applicants specification. The art cited does not meet this requirement. As discussed above, a traumatic CNS injury produces multiple physiological events that lead to the neurodegeneration. Simply the fact that progesterone metabolites interact with the GABA receptor (as taught by Gee *et al.*) is insufficient to render obvious the use of allopregnanolone for the successful treatment of traumatic central nervous system injuries or for decreasing neurodegeneration on a population of cells in a subject following a traumatic injury to the CNS as claimed by the instant invention. None of the cited references would guide one of skill in the art to select allopregnanolone, among the multitude of progesterone metabolites, and administer this compound to a subject having a traumatic CNS injury.

The Examiner is reminded that the prior art itself must provide the skilled artisan the motivation to make the claimed invention. In the present case, the Examiner has merely used Applicant's claims as a guide and selected references at random that mention various aspects of

NO

the claimed invention. This is an improper standard. "One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." *In re Fine*, 837 F.2d 1071, 1075, 5 USPQ 2d 1596, 1600 (Fed. Cir. 1988). The law is clear that without motivation to combine the references, a rejection under 35 USC §103 fails.

Moreover, a *prima facie* case of obviousness requires that the art convey to one of skill that there is a reasonable expectation of success. The cited prior art fails to provide a reasonable expectation that the administration of allopregnanolone to a subject would successfully treat a traumatic CNS injury or decrease neurodegeneration as claimed by the instant invention. First, the guidance provided by the cited art must be sufficiently specific to direct the attention of one skilled in the art to the selection of parameters and choices necessary to obtain the claimed invention. While, Gee *et al.* demonstrates that progesterone metabolites, such as allopregnanolone, interact with the $GABA_A$ receptor, none of the references cited demonstrate that modulation of $GABA_A$ is sufficient to treat a subject following a traumatic CNS injury. As discussed above, the initial impact of a CNS trauma produces many physiological events, including the disruption of multiple receptors/neurotransmitters. Therefore modulating the activity of a single receptor is hardly sufficient to provide a reasonable expectation that allopregnanolone would successfully treat the traumatic CNS injury that is accompanied by a vast number of physiological events. Thus, the art cited by the Examiner offers nothing more than the understanding that certain progesterone metabolites can interact with GABA receptors and that administration of progesterone to rats improves the physiological outcome of traumatic brain injury. Consequently, the prior art offers no suggestion or expressed expectation that administration of allopregnanolone would successfully treat a traumatic brain injury.

The Examiner's attention is drawn to pages 20-32 of the specification which demonstrates for the first time that following a traumatic central nervous system injury, the administration of allopregnanolone significantly reduces cerebral edema when compared to control rats (see Figure 1); significantly increases the learning rate compared to control rats (See Figure 2); and, significantly delays the synthesis and level of activity of inflammatory cytokines (Figures 3 and 4). Consequently, prior to the present invention, one of skill in the art would not have recognize

Not unexpected
NO comparison

that allopregnanolone could be used to treat a traumatic CNS injury or decrease neurodegeneration as claimed by the present invention.

In summary, the Examiner has failed to establish a *prima facie* case of obviousness. As discussed above, Roof *et al.* (1992), Roof *et al.* (1994), Roof *et al.* (1997), and Gee *et al.* offer no suggestion to administer allopregnanolone to a subject following a traumatic CNS injury and moreover, fail to provide a reasonable expectation of success. Accordingly, Applicants respectfully submit that the claimed methods are not obvious in view of the cited references and respectfully request that the rejection of claims 1-20 under 35 U.S.C. § 103(a) be withdrawn.

CONCLUSIONS

Accordingly, in view of the above remarks, it is submitted that this application is now ready for allowance. Early notice to this effect is solicited.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

Kelly J. Williamson

Kelly J. Williamson
Registration No. 47,179

Customer No. 00826
ALSTON & BIRD LLP
Bank of America Plaza
101 South Tryon Street, Suite 4000
Charlotte, NC 28280-4000
Tel Raleigh Office (919) 862-2200
Fax Raleigh Office (919) 862-2260

In re: Stein, *et al.*
Appl. No.: 09/973,375
Filed: 10/09/01
Page 6 of 6

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